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Autoreferát disertační práce

Korelace mezi kvantitativními in vivo MR parametry v různých tkáních (MR spektroskopické zobrazování, MR difúzometrie, MR relaxometrie aj.)

Mgr. Dita Wagnerová

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Předseda oborové rady:	Prof. MUDr. RNDr. Jiří Beneš, DrSc.
Školící pracoviště:	MR oddělení, Pracoviště radiodiagnostiky a intervenční radiologie Institut klinické a experimentální medicíny Praha
Školitel:	Ing. Milan Hájek, DrSc.

Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

Charles University in Prague

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Summary of Doctoral Thesis

Correlation between quantitative MR parameters in various tissues in vivo (MR spectroscopic imaging, MR diffusometry, MR relaxometry)

Mgr. Dita Wagnerová

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Doctoral studies in biomedicine

Charles University in Prague and the Academy of Sciences of the Czech Republic

Study programme:	Medical Biophysics
Board chairperson:	Prof. MUDr. RNDr. Jiří Beneš, DrSc.
Training workplace:	MR Unit, Department of Diagnostic and Interventional Radiology Institute for Clinical and Experimental Medicine in Prague
Thesis Supervisor:	Ing. Milan Hájek, DrSc.

Contents

Abstrakt

Koregistrace MR spektroskopických (SI), difúzních (DTI) a relaxačních obrazů a jejich následné korelace založené na kvantitativním zpracování obrazu bod po bodu mají potenciál rozlišit patologické stavy a zdravou tkáň, a pomoci tak stanovit rozsah patologie. Použití této metody v klinické praxi bylo vyzkoušeno u pacientů s tumorem mozku a s temporální epilepsií (TLE).

30 pacientů s nově diagnostikovanou lézí, 22 pacientů s léčeným tumorem (diagnóza stanovena na základě histologie či radiologickým sledováním), 20 pacientů s TLE a 59 zdravých dobrovolníků bylo vyšetřeno v magnetickém poli 3T. Vyšetřovací protokol obsahoval T2-vážené MR obrazy, SI, DTI a T2 relaxometrii. Korelace byly analyzovány programem CORIMA umožňující automatickou identifikaci oblasti zdravé tkáně dle kontrolních dat.

Mozkové léze: Specifické tvary korelací metabolitů, MD a T2 relaxačních časů (T2) byly nalezeny pro danou lokalizaci léze i pro daný typ tumoru. Tyto korelace vznikají v důsledku zastoupení různých typů tkání ve zkoumané oblasti. Korelační grafy rekurentních tumorů vykazovaly charakteristiku stejnou jako u tumorů neléčených, ale se změněnými hodnotami parametrů vlivem terapie. Metabolické hodnoty nekorelovaly s MD nebo T2 v případě radiační nekrózy.

TLE: V hipokampu v předozadním směru se MR parametry měnily postupně u všech subjektů, nicméně směrnice závislosti u pacientů statisticky významně překračovala hodnoty naměřené u kontrol.

Pro diferenciaci tkáně jsou vhodné korelace mezi následujícími parametry: MD, T2, cholin, kreatin, N-acetylaspartát, inositol, laktát, makromolekuly, lipidy a jejich poměry.

Kvantitativní zpracování různých MR obrazů umožňuje komplexně popsat vysoce heterogenní tkáň v patologii a jejím okolí a určit důležité parametry pro tkáňovou diferenciaci a stanovení rozsahu patologie.

Abstract

Coregistration of MR spectroscopic (SI), diffusion (DTI), relaxation images and their subsequent correlations based on pixel-by-pixel quantitative analysis have the potential to distinguish between pathological states and healthy tissue and therefore can help assessing brain pathology extent. Patients with brain tumours and temporal lobe epilepsy (TLE) were involved in the study to validate the use of this method in clinical practice.

30 patients with a new diagnosed brain lesion, 22 patients with a treated tumour (diagnosis assessed by histology or by radiological follow-up), 20 TLE patients and 59 healthy subjects were examined on a 3T system. The measurement protocol consisted of T2-weighted MR images, SI, DTI and T2 relaxometry. Correlations were analysed with the CORIMA programme with automatic identification of pixels in the normal tissue according to control data.

Brain lesions: Specific correlation patterns between metabolites, MD and T2 relaxation times (T2) were found for a given lesion localisation and tumour type. The patterns depend on different tissue states involved in the examined area. Recurrent tumours exhibited the same patterns as untreated ones but with changed parameter values caused by therapy. Metabolic values did not correlate with MD and T2 in radiation necrosis.

TLE: MR parameters gradually changed in anteroposterior direction of HC in all subjects; however, slopes in patients significantly exceeded those in controls.

Correlations of the following MR parameters are suitable for tissue differentiation: MD, T2, choline, N-acetylaspartate, creatine, inositol, lactate, macromolecules, lipids and their ratios.

A quantitative analysis of different MR methods is able to describe the complexity of a highly heterogeneous tissue in the pathology and its vicinity and determine crucial parameters for tissue differentiation and lesion extension.

1 Introduction

Magnetic resonance imaging (MRI) has become a major non-invasive tool for examination of diseases of the central nervous system. However, conventional MRI is unable to study biochemical and functional features of the examined tissue. This drawback led to the development of more sophisticated MR methods such as proton MR spectroscopic imaging (1H MRSI), diffusion imaging (DWI) or MR relaxometry [1]. MR relaxometry quantifies relaxation times which are responsible for tissue contrast in MRI. 1H MRSI provides information about the metabolic profile of the tissue in vivo which is useful for pathology differentiation in both neurology and neurooncology. Diffusion measurements enable the examination of the tissue microstructure and molecular dynamics of water in the extracellular compartments. DWI is widely used to distinguish tumours from bacterial abscess, to increase a specificity of lymphoma detection or to diagnose an acute ischemia.

A qualitative description of radiological images is common now in clinical practice; however, it has been revealed that combination of different diagnostic and quantitative methods provides more precise information of the nature and extent of pathology in various diseases (differential diagnosis of human brain tumour and radiation necrosis, epileptic and neurodegenerative disorders, etc.). As metabolic, diffusion and relaxation maps represent complementary pieces of information [2-7], their coregistration and subsequent correlations based on pixel-by-pixel analysis have been found useful in distinguishing pathological states (tumour, oedema, oedema infiltrated by tumour, oedema, necrosis) and a healthy tissue in individual patients at 1.5T. The knowledge of structural, biochemical and functional information is crucial for the best therapy planning and improvement of patient prognosis.

Human brain tumours represent a heterogeneous group of pathologies. The most frequent brain tumours are gliomas. Several regions with different cell

density, metabolism and structure are found within the pathology resulting in various levels of spectroscopic, diffusion and relaxation parameters. In general, tumours exhibit decreased N-acetylaspartate (NAA), creatine (Cr) and elevated choline (Cho), inositols, lactate, mean diffusivity (MD) and T1 and T2 relaxation times (T1, T2 resp.).

Temporal lobe epilepsy (TLE) is surgically-remediable drug-resistant focal epilepsy. The most common subtype of TLE is the syndrome of mesial temporal lobe epilepsy (MTLE) where epileptic seizures originate from the mesial structures. Symptomatic TLE is aetiologically divided into MTLE associated with hippocampal sclerosis (HS), lesional TLE caused by different structural lesions, and cryptogenic TLE [8]. The epileptogenic zone in MTLE is usually characterised by hippocampal structural changes resulting in increased MD and T2, neuronal dysfunction (decreased NAA), reactive astrogliosis (increased Cr) and dysplastic cortical lesions (increased Cho).

Although these two diseases are not related from the point of view of aetiology, the only available treatment is neurochirurgical resection of the pathology and, consequently, complex information describing the nature and extent of the pathology is crucial.

A prospective quantitative MR study of patients suffering from brain tumours and patients with drug-resistant temporal lobe epilepsy has been performed in magnetic field 3T to validate the quantitative techniques and demonstrate their potential use in the clinical routine.

2 Hypothesis and aims of the thesis

The aim of this thesis was to develop a methodology combining standard MR imaging, MR spectroscopic imaging, diffusion tensor imaging, T1 and T2 MR relaxometry for evaluating the spatial distribution of pathology in magnetic field 3T and validate it with patients suffering from brain tumours and drug-resistant temporal lobe epilepsy. Each MR parameter represents distinct phenomena and different methods can reveal the differences in pathology extent. Therefore, the combination of different MR methods and their quantitative evaluation at once has the potential to increase the specificity of diagnosing the pathology tissue state and tumour grading. Consequently, an exact quantitative evaluation can help improve the outcome of patients.

Several particular aspects of the use of combination of different MR methods have been addressed:

1. Development of software enabling pixel-by-pixel image analysis and automatic creation of mutual relationships (correlations) between individual quantitative MR parameters.
2. The use of the correlations for tissue differentiation in patients with different types of new diagnosed brain lesions, demonstration of their potential use in the clinical routine and its comparison with histopathological findings provided by image-guided stereotactic biopsy.
3. The use of the combination of different methods for differential diagnosis between tumour recurrence and radiation necrosis in irradiated patients after lesions resection and its benefit in neurooncological practice.
4. The use of correlations between individual quantitative MR parameters to assess hippocampal involvement in patients with drug-resistant temporal lobe epilepsy and comparison with standard clinical diagnostic protocols.

3 Materials and Methods

Fifty-two patients involved in the study of brain lesions were divided into two groups. Group 1 consisted of 30 patients with a new diagnosed lesion. Group 2 consisted of 22 patients with suspicion of a tumour recurrence and/or radiation necrosis. The mean age was 49.1 ± 15.3 years. Twenty TLE patients (mean age 29.6 ± 12.4 years) considered for resective surgery for intractable epilepsy were involved in the epilepsy study. Fifty-nine healthy subjects were included in these studies as controls. The mean age was 34.3 ± 13.4 years.

A diagnosis of patients was subsequently assessed by histopathology or radiological follow-up.

The patients underwent a standard clinical examination protocol at 1.5T. These images were not included in the quantitative analysis. Consequently, they were examined on a 3T scanner equipped with a transmit-receive head coil. The examination protocol included MRI, diffusion tensor imaging (DTI; 20 directions, b=0,1000s/mm^2, resolution 2x2x2.5 mm^3), 2D and/or 3D MRSI (echo time 30 and/or 135 ms, resolution 10x10x15 mm^3 or 10x10x5.6 mm^3), T2 relaxometry (32 echoes, resolution 0.78x0.78x5 mm^3) and/or T1 relaxometry (7 echoes, resolution 0.78x0.78x15 mm^3).

MRSI data were analysed using the jSIPRO programme [9] with a graphical LCModel-SI data interface. Data processing included mild k-space filtering and zero filling to a 32x32 matrix size. Water signal was used as an internal standard for the calculation of metabolic concentration in laboratory units. DTI data were processed with FSL program. Corrections for eddy currents and motion artefacts were used. Relaxation maps were calculated using the in-house program ViDi utilising a three-parameter fit.

Correlations and regression analysis were performed using the interactive CORIMA programme developed as a part of the thesis [3, 10]. This programme enables the automatic identification of pixels in the normal tissue according to

control data. The correlations were based on a pixel-by-pixel evaluation of two different MR methods. The software allows the manual selection of a region of interest (ROI) in one map (metabolite, relaxation, or diffusion) and automatically finds the corresponding region in another map. The correlations are then calculated from this selected ROI. Each point in the correlation plot corresponds to one pixel in the MR images. Additionally, it is possible to select a group of points in the correlation plot and highlight corresponding pixels in MR images. Several ROIs were examined in each subject. Assuming the tumour properties change from tumour core towards its margins [4], the ROIs were selected as narrow strips oriented radially from the tumour core. Accordingly, the ROIs include a tumour tissue as well as a possible oedematous, tumour infiltrated and healthy tissue. In the case of epileptic patients, regions of both hippocampi (HC) were evaluated separately in each subject. The metabolic maps as well as the maps of metabolic ratios were used. All control data were divided into several groups according to subjects' age and measured regions. The minimum (MIN) and maximum (MAX) values for each parameter and each region were assessed. These intervals represented control data used later for the semiautomatic evaluation of patients' data for each image modality. These confidence intervals were highlighted in the patients' correlation plots by shading and bordering by blue lines. Every point inside this interval was highlighted automatically in the evaluating images and was interpreted as representing healthy tissue. The regions out of this confidence interval were considered as pathologic. In the case of epileptic patients, significant changes in both HC were interpreted as bilateral pathology. A linear fit was used for the correlation analysis. Mann-Whitney U-test was used for comparison of correlation slopes between different patient groups and controls.

4 Results

The CORIMA programme for automated coregistration and parameter correlations was developed and tested on healthy controls' and patients' data.

4.1 Healthy controls

Significant differences of metabolite, MD, T2 and T1 values were found in different parts of the brain. The parameter values, especially metabolites, were age depended. If the regions were examined separately, no significant correlations between metabolite concentrations and MD, T2 or T1 were found in any control subgroups except the hippocampus. No significant differences were found between the corresponding regions in the right and left hemisphere. NAA and T2 (MD) revealed negative correlations in the hippocampi. Cr/NAA, Cho/Cr, Cho/NAA and Cho correlated positively with T2 or MD (see Figure 1). Cr-T2 and Cr-MD did not correlate. MD, T2, Cho, Cr/NAA, Cho/Cr, Cho/NAA gradually decreased and NAA gradually increased in the anteroposterior direction of the hippocampus.

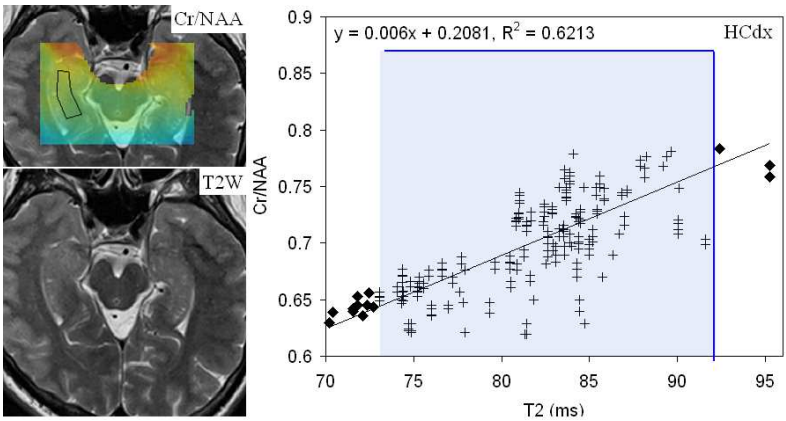

Figure 1 The Cr/NAA-T2 correlation in hippocampi in a 24 year-old healthy control. Each cross represents an ordered pair of Cr/NAA and T2 values corresponding to one pixel in the analysed area. All the values outside the control interval (blue shaded) are visible as diamonds. T2W, T2-weighted image; Cr, total creatine; NAA, total N-acetylaspartate; T2, T2 relaxation time; HCdx, right hippocampus.

The control values were used for automatic separation of healthy tissue in each patient using the CORIMA programme.

4.2 Patients with a brain tumour

Different correlation patterns between metabolites, MD and T2 were found at 3T not only for different lesion localisation but also for different tumour types. Low grade gliomas (LGG), high grade gliomas (HGG) and lymphomas (LYM) revealed specific correlation patterns characterising structural and metabolic changes in each tumour type. The origin of these patterns (Figure 2, pattern A in LGG, C in HGG and E in LYM) is based on different tissue states involved in an examined area, i.e. healthy tissue (region 1), tissue infiltrated by tumorous cells (2), active tumour (3), tumour infiltrated oedema (4), oedema (5), etc. The positive linear MD-T2 correlation was found in LGG and LYM (Fig.2, patterns B, D), not in HGG containing a dense non-enhancing tissue (pattern F). The dense non-enhancing tissue is characterised by low MD and high T2, whereas LGG revealed high MD and high T2 and lymphomas low MD and low T2. Differences of correlation patterns in different directions within one lesion were found. It therefore provided information about the tissue state in a selected direction and enabled detection of the growth direction of the primary tumour. More heterogeneous regions such as the basal ganglia, hippocampi, etc. invoked more complicated correlations with similar correlation trends as in other regions but with additional clusters in the standard plots.

Recurrent tumours exhibited the same correlation patterns as untreated ones but with changed metabolic values caused by radiation/chemotherapy. Cho values in recurrent tumours were lower than values in untreated ones. Slightly increased Cho and low NAA values were found in healthy tissue in the peri-cavity region compared to control data. Metabolic values do not correlate with MD and T2 in the tissue with radiation changes only.

Correlations of the following MR parameters are suitable for tissue differentiation: MD, T2, Cho, NAA, Cr, inositol, lactate, macromolecules and lipids and metabolite ratios.

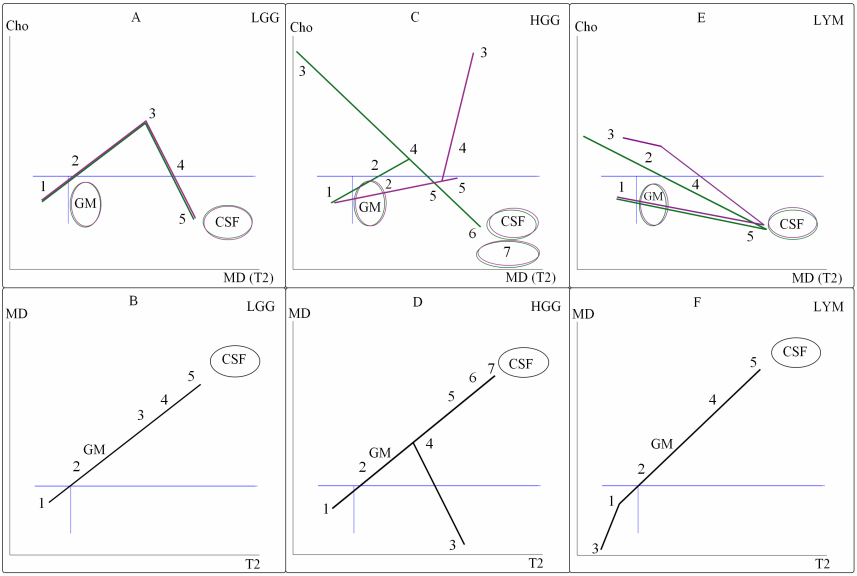

Figure 2 Schematic correlations in LGG, HGG and LYM. Cho-MD (green), Cho-T2 (violet) correlations are in the first row, MD-T2 in the second one. Region 1 corresponds to a healthy tissue; 2, infiltrative tumour; 3, active tumour; 4, tumour infiltrated oedema; 5, oedema; 6, tumour/ necrosis; 7, necrosis; GM, grey matter; CSF, cerebrospinal fluid.

Standard voxel-based MRS evaluation was found suitable for differential diagnosis (DD) between tumour recurrence and radionecrosis. The recurrent tumours always exhibited high Cho and Cho/Cr (Fig.3). Cho and Cho/Cr values were higher in HGG than in LGG. A tissue with radionecrosis revealed lower Cho and Cho/Cr values and higher Lac compared to tumour recurrence. Different Cr levels, low NAA and high Cho/NAA were observed in both types of lesions. The Cho/Cr ratio was found the most useful parameter for DD between both lesion types. The sensitivity of MRS reached 85 % and the specificity 91 % compared to histopathological and neuroradiological results.

The examination protocol for MRSI-navigated biopsies has been successfully implemented into the neurooncological navigated systems.

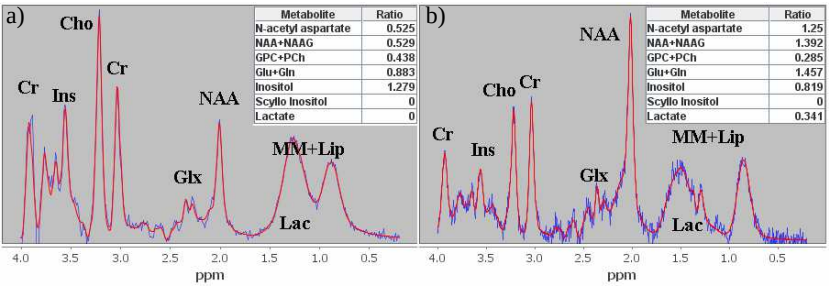

Figure 3 Short echo time spectra a) from recurrent tumour (oligodendroglioma III) and b) from the tissue changed by radiation. Tables contain ratios between stated metabolites and total creatine.
Cho, GPC+PCh, choline-containing compounds; NAA+NAAG, NAA, total N-acetylaspartate; Cr, total creatine; Glx, Glu+Gln, glutamine and glutamate; Ins, myo-inositol; Lac, lactate; MM+Lip, macromolecules and lipids.

4.3 Patients with temporal lobe epilepsy

MD, T2, Cho, Cr/NAA, Cho/Cr, Cho/NAA gradually decreased and NAA gradually increased in the anteroposterior direction of the hippocampus in all subjects similarly as in controls. Correlations in the pathologic HC are listed in Table 1. Slopes of MRS-T2 dependence were significantly higher in patients than in controls ($p<0.05$), but did not differ between both patient groups. The difference is caused by substantial metabolic changes in patients. The T2 and MD values are within the control intervals in case of non-lesional TLE. Histologically proven HS and gliosis exhibited increased T2 values compared to healthy controls; however, other lesions exhibited even more T2 increment. The semiautomatic evaluation based on control MRS-T2 data correctly lateralised EZ in all unilateral cases and the predominance in all bilateral cases. MRS-MD data correctly lateralised EZ in all unilateral cases, but failed in two bilateral cases.

	Con	N-les HC	Les HC
MD-T2	P	P	P
Cho-T2 (MD)	P	P	P
Cr/NAA-T2 (MD)	P	P	P
Cho/Cr-T2 (MD)	P	Ø	P
Cho/NAA-T2 (MD)	P	P	P
NAA-T2 (MD)	N	N	N
Cr-T2 (MD)	Ø	P	P

Table 1 Correlations between selected parameters in controls and abnormal hippocampi in patients with MTLE.
Con, controls; N-les HC, non-lesional hippocampus; Les HC, lesional HC; MD, mean diffusivity; T2, T2 relaxation times; Cho, total choline; Cr, total creatine; NAA, total N-acetylaspartate; P, positive correlation; N, negative; Ø, no correlation.

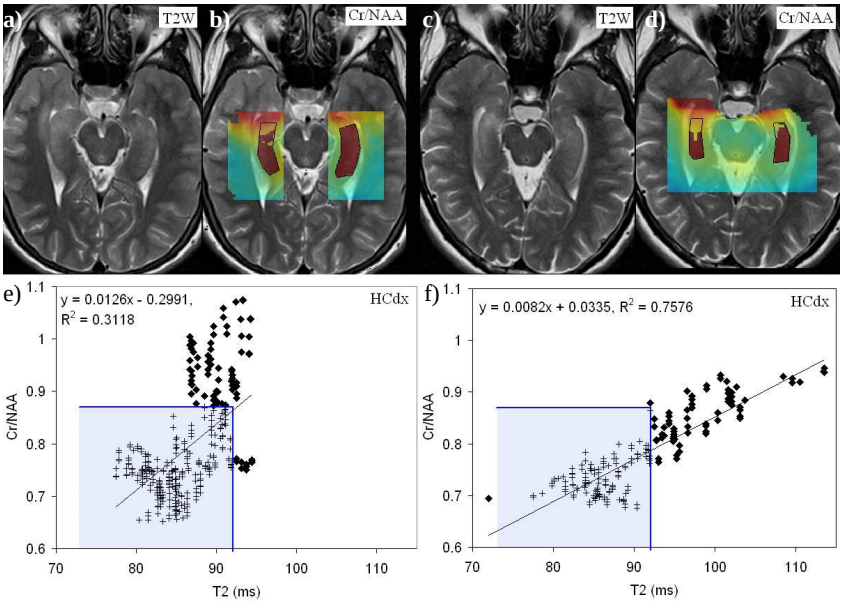

Figure 4 The Cr/NAA-T2 correlation in hippocampi in a patient with MTLE without HS and in a patient with HS.
a,c) T2-weighted images parallel to the long HC axis. b,d) Cr/NAA maps positioned on T2W images with the maximal value of the Cramer-Rao bound of total Cr/NAA ratios set to 15%. Red pixels inside the selected area in each hippocampus on Cr/NAA maps correspond to the healthy tissue according to control data. e,f) Each cross represents an ordered pair of Cr/NAA-T2 values corresponding to one pixel in the analysed area. All the values outside the control interval (blue shaded) visible as diamonds correspond to tissue abnormalities. According to semiautomatic quantitative evaluation, the anterior portion of the right hippocampus in both patients showed an abnormal finding whereas the left hippocampi have normal findings (correlations not shown). T2W, T2 weighted image, Cr, total creatine, NAA, total N-acetylaspartate, HCdx, right hippocampus.

5 Discussion

The combination of MR parameters often creates complicated correlation patterns. Nevertheless, their analysis provides unique information about the abnormal tissue and pathology extension. Our method is based on the fact that, although tissues in different conditions may reveal similar values in individual parameters, they create separated characteristic clusters in the correlation plot which consequently enable their differentiation [10]. Previous studies reported the use of Cho-MD correlations for tissue differentiation in tumours [3,4]; however, we found that even a combination of these two parameters was insufficient. The set of different correlations should be considered as a whole.

If pathology extent is a matter of interest, the correlations represent a unique method for tissue differentiation. However, as the standard voxel-based evaluation is not so time consuming, it represents a method of choice in EZ lateralisation in MTLE patients and in the assessment of DD between radiation necrosis and tumour recurrence. In irradiated patients, Cho/Cr and Lac/Cr were found the most reliable predictors of pathologies as Cr was less sensitive to therapy than NAA. Even so, the existence of correlations in heterogeneous region (such as the tumorous and irradiated tissue or HC) requires a comparison of the patients' and controls' data in the same part of the brain [11]. As the studied MR parameters gradually change, standard statistical methods based on a comparison of their averaged values fail in a detailed description of the tissue due to substantial data dispersion related to physiological properties. Therefore, the correlations may better describe the relation between the parameters and physiology and provide important information related to pathology extent.

Although quantitative data analysis seems to be a promising tool, several technical difficulties, such as diffusion image distortions, chemical shift artefact or bad spectra quality may significantly influence the mutual relations. For that reason, this method should be used only in semiautomatic mode.

6 Summary

Progress in MR techniques and in computer technology has revealed that a combination of different diagnostic methods may provide more precise information of the nature and extent of brain pathology. However, patient outcomes after neurosurgeries have shown that qualitative image evaluation is not always precise enough in the assessment of pathology extent. Hence, a new quantitative method combining metabolic, diffusion and relaxation images was developed and its potential clinical use was demonstrated in patients with brain tumours and temporal lobe epilepsy.

This study summarises the MR features (metabolite levels, diffusion coefficients and relaxation times) in different parts of a healthy human brain and in different brain pathologies. The parameter values in a healthy brain were found region and age dependent; therefore, both age and region matched control data is necessary to use for automatic assessment of a healthy tissue in the patients. Correlation patterns depend on tissue involved in an examined area and are specific for each tumour type. For that reason, quantitative image analysis can be used for both tumour and tissue differentiation and this knowledge can be used in neurosurgery and therapy planning. Recurrent tumours exhibit the same correlation patterns as untreated ones. However, automatic assessment of healthy tissue was not precise enough as parameter values in the surrounding tissue were changed by chemo/radiotherapy and they did not reach the control values. No correlation between metabolic values and MD or T2 was found in the tissue with radiation changes only. Correlations between MD, T2 and Cho, NAA, Cr, myo-inositol, lactate, macromolecules, lipids, their ratios are suitable for tumorous tissue differentiation. This study establishes that a combination of different MR parameters may help in better identification of the tumour type, examination of the tumour extension,

direction of proliferation and also in better understanding of biochemical processes inside the tumour.

Standard voxel-based evaluation of MRSI data was found to be the method of choice in differential diagnosis between tumour recurrence and radiation necrosis. The MRS diagnosis was in agreement with the final diagnosis in 88 % of irradiated cases. MRSI-navigated biopsies enable targeting the regions with the most significant metabolic changes and therefore help to assess the diagnosis more precisely in the case of multiple or large lesions.

Mutual relations between studied parameters in hippocampus in patients with TLE revealed gradual changes in individual parameters in the anteroposterior direction of the hippocampus providing additional information about spatial distribution of these parameters across the hippocampus. Correlation patterns significantly differed between controls and patients. The slope provides information about the significance of metabolic or structural changes. The correlations with relaxation times were found more precise for assessment of hippocampal involvement than correlation with MD, principally because of distortions in diffusion images. Correlations between T2 and Cho/NAA, Cr/NAA, Cr/Cho, Cho, NAA are suitable for correct lateralisation.

This study confirmed the value of combining different neuroimaging methods in surgical planning in cases with inconsistent lateralisation; however, single voxel spectroscopy over the larger volume of the hippocampus may be sufficient for basic EZ lateralisation.

Although the technique can be used only in the semiautomatic mode due to an unavoidable chemical shift artefact in MRSI and image distortions in DTI, we proved that the combination of different MR parameters is able to describe the complexity of a highly heterogeneous tissue in various pathologies and in their vicinity.

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8 List of publications

1. Publications and manuscripts the thesis is based on

   a) with impact factor

   Wagnerova D, Herynek V, Malucelli A, Dezortova M, Vymazal J, et al. Quantitative MR imaging and spectroscopy of brain tumours: a step forward? Eur Radiol 2012; 22(11):2307-2318. IF2011: 3.222

   Wagnerova D, Jiru F, Dezortova M, Vargova L, Sykova E, Hajek M. The correlation between 1H MRS Choline concentrations and MR diffusion trace values in human brain tumours, Magn Reson Mater Phy 2009; 22(1):19-31. IF: 1.859

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   Wagnerová D, Herynek V, Dezortová M, Marusič P, Kršek P, Zámečník J, Jírů F, Škoch A, Hájek M. Using of correlations between quantitative MR parameters for assessment of hippocampal involvement in temporal lobe epilepsy. Submitted to Eur Radiol. IF2011: 3.222

2. Other publications

   a) with impact factor

   Herynek V, **Wagnerova D**, Hejlova I, Dezortova M, Hajek M. Changes in the brain during long-term follow-up after liver transplantation. J Magn Reson Imaging 2012; 35:1332-1337. IF2011: 2.698

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b) without impact factor

Hájek M, Dezortová M, **Wagnerová D**, Voska L, Hejlová I, Trunečka P. Stanovení obsahu jaterního tuku metodou 1H MR spektroskopie. Čas Lék čes 2011; 150:68-71

Saudek E, Novak D, **Wagnerova D**, Hajek M. Analysis of Human Brain NMR Spectra in Vivo Using Artificial Neural Networks, Lect Notes Comp Sc 2008; 5164:517-526

Total impact factor: 9.941